Catecholamine Function in Posttraumatic Stress Disorder: Emerging Concepts

Edited by
M. Michele Murburg, M.D.

Washington, DC
London, England

Note: The authors have worked to ensure that all information in this book concerning drug dosages, schedules, and routes of administration is accurate as of the time of publication and consistent with standards set by the U.S. Food and Drug Administration and the general medical community. As medical research and practice advance, however, therapeutic standards may change. For this reason and because human and mechanical errors sometimes occur, we recommend that readers follow the advice of a physician who is directly involved in their care or in the care of a member of their family.

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Chapter 1

Biology of Catecholaminergic Systems and Their Relevance to PTSD

M. Michele Murburg, M.D.
E. Alexandra Ashleigh, M.D.
Daniel W. Hommer, M.D.
Richard C. Veith, M.D.

In an effort to make this book "user-friendly" to readers from a variety of disciplines, we provide in this chapter some background information not given elsewhere in this volume on both the biology of catecholaminergic systems and the phenomenology of posttraumatic stress disorder (PTSD). The information presented below is not meant to be an exhaustive treatment of any of the topics discussed, and readers who would like further details may want to consult some of the sources referenced herein. A description of peripheral catecholamines and the sympathetic nervous system (SNS) is provided in Chapter 16 by Drs. Veith and Murburg.

SYNTHESIS, STORAGE, RELEASE, METABOLISM, AND REUPTAKE OF CATECHOLAMINES

The catecholamines that act as neurotransmitters in mammalian central and peripheral nervous systems are the related compounds dopamine, norepinephrine, and epinephrine. As shown in Figure 1–1, dopamine is formed from the amino acid precursor tyrosine and in turn serves as a precursor for norepinephrine, which may be transformed into epinephrine (Nagatsu et al.

1964). The reactions by which each of these compounds is formed occur in the brain, sympathetic nerves and ganglia, the heart and arterial and venous tissue, and the adrenal medulla (Cooper et al. 1991). Because each step in the synthesis of these compounds is catalyzed by a specific enzyme, the profile of catecholamine end products synthesized in a particular tissue reflects, in part, the relative expression of genes for those enzymes in that tissue under a given set of conditions. Catecholamine synthesis may thus be regulated by a variety of factors influencing enzyme synthesis and activity. For example, catecholamines exert feedback inhibition over tyrosine hydroxylase activity (Nagatsu et al. 1964), while steroid hormones increase phenylethanolamine-N-methyltransferase activity (Cooper et al. 1986). Other factors, including the availability of tyrosine substrate, may be important under certain conditions such as increased neuronal impulse flow (Milner and Wurtman 1986).

Once synthesized, catecholamines are stored in specialized storage vesicles, or granules, in sympathetic nerve endings, chromaffin cells, and central nervous system (CNS) catecholaminer-

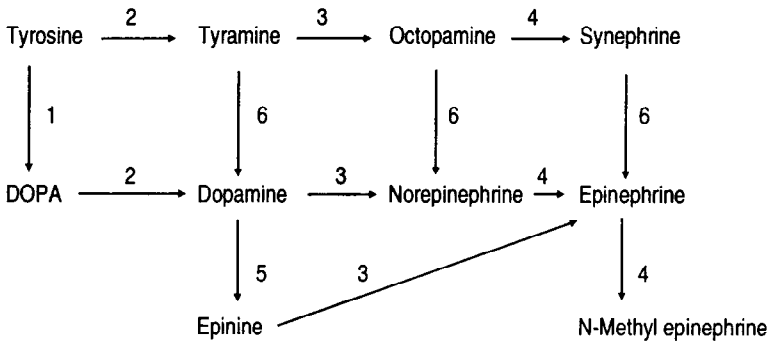

Figure 1–1. Synthesis of catecholamines. 1, tyrosine hydroxylase; 2, aromatic amino acid decarboxylase; 3, dopamine ß-hydroxylase; 4, phenylethanolamine-N-methyltransferase; 5, nonspecific N-methyltransferase in lung/folate-dependent N-methyltransferase in brain; 6, catechol-forming enzyme. DOPA = dihydroxyphenylalanine. For a full discussion, see Cooper et al. 1991.

gic neurons (Hillarp et al. 1953). These storage vesicles protect the catecholamines from degradation by intraneuronal enzymes such as monoamine oxidase (MAO) (see Carlsson 1987 for review), and then permit them to be released upon depolarization of the nerve cell. Release of catecholamines from nerve terminals is subject to local feedback inhibition by catecholamines acting at presynaptic autoreceptors, and also by the actions of certain other neurotransmitters, neuropeptides, and prostaglandins (see Cooper et al. 1991 for review).

The catecholamines undergo metabolic degradation by the enzymes MAO and catechol-O-methyltransferase (COMT) (for review, see Axelrod 1973; Carlsson 1987). The products of catecholamine metabolism are shown in Figures 1–2 and 1–3. In

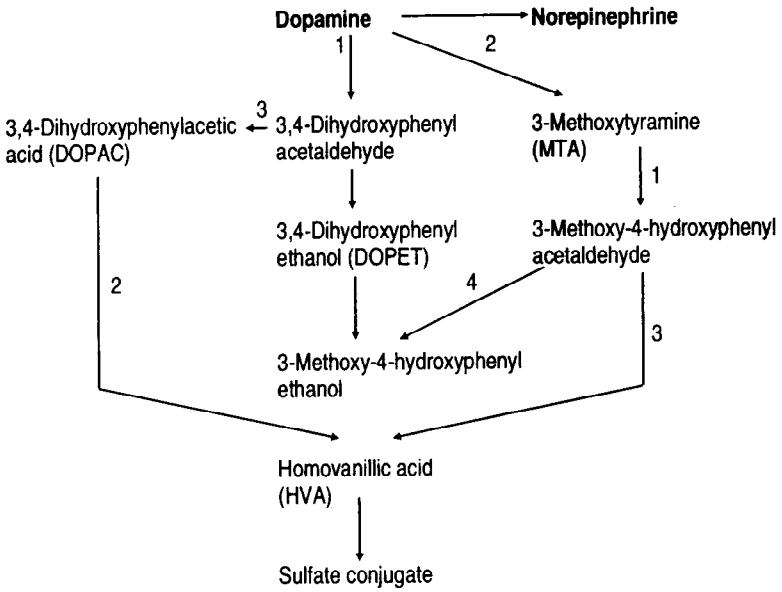

Figure 1–2. Metabolism of dopamine. 1, monoamine oxidase (MAO); 2, catechol-O-methyltransferase (COMT); 3, aldehyde dehydrogenase; 4, aldehyde reductase. For a full discussion, see Cooper et al. 1991.

addition to inactivation by metabolic degradation, catecholamine activity at the synapse is terminated by an active, energy-dependent process called *reuptake,* whereby neurotransmitters are taken back into the presynaptic nerve terminals and then into the storage granules (Axelrod 1973; Carlsson 1987; Cooper et al. 1986). Reuptake and enzymatic degradation are important mechanisms in both the CNS and the peripheral SNS for removal of active catecholamine neurotransmitter from the synaptic terminal areas. In addition, catecholamines released from SNS neurons into the bloodstream are removed from circulation by the kidneys.

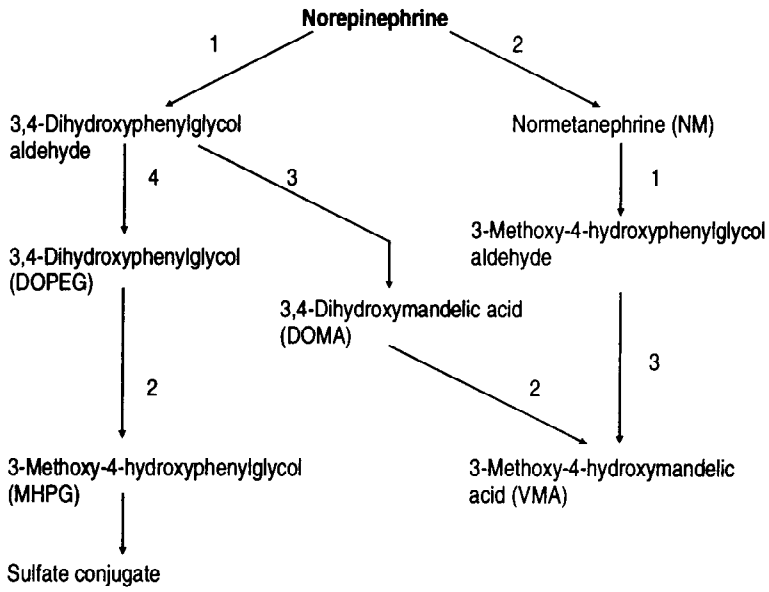

Figure 1–3. Metabolism of norepinephrine. 1, monoamine oxidase (MAO); 2, catechol-O-methyltransferase (COMT); 3, aldehyde dehydrogenase; 4, aldehyde reductase. For a full discussion, see Cooper et al. 1991.

CATECHOLAMINE-RECEPTOR INTERACTIONS

Like other neurotransmitters, catecholamines exert their effects on target cells by binding to receptors, or specialized macromolecules on the surface of the postsynaptic cell membrane, that recognize specific transmitters. This binding then triggers a number of effects on the target cell through a series of *postreceptor* mechanisms. Norepinephrine and epinephrine bind to several subtypes of adrenergic receptors, referred to as α_{1A}, α_{1B}, α_{2A}, α_{2B}, α_{2C}, and $ß_1$, $ß_2$, and $ß_3$ (Harrison et al. 1991; see Lerer et al., Chapter 13, this volume, for a full discussion). Dopamine binds to a family of receptors (D_{1A}, D_{1B}, D_{2A}, D_{2B}, D_3, D_4, D_5) (see Strange 1991 for review; Sunahara et al. 1991). These receptors are coupled via guanine nucleotide-binding proteins to second messenger systems such as adenylate cyclase/cyclic AMP or phosphatidylinositol. Binding of the catecholamine to the receptor results in either activation or inhibition of such second messenger systems (see Lerer et al., Chapter 13, this volume), which in turn regulate intracellular calcium mobilization and protein kinase C activation (Berridge 1984a, 1984b; Nishizuka 1984). These "third messengers" in turn affect neuronal activity, gene expression, and protein activation. In general, β and D_1 receptors stimulate adenylate cyclase, α_2 and D_2 receptors inhibit adenylate cyclase, and α_1 receptors stimulate hydrolysis of phosphatidylinositol (see Cooper et al. 1986 for review).

FUNCTIONAL ANATOMY OF CENTRAL CATECHOLAMINERGIC SYSTEMS

Norepinephrine

The brain's major noradrenergic nucleus is the locus coeruleus (LC), a cell group in the central gray of the caudal pons. From the LC, fibers course through five major tracts to innervate structures throughout the neuraxis such as the brain stem, neocortex, hypothalamus, cerebellum, spinal cord (including parasympathetic nuclei), amygdala, and hippocampus, among many others (for reviews, see Aston-Jones et al., Chapter 2, this volume; Murburg et al. 1990). The structures to which the LC projects include areas

known to participate in responses to fear and pain, as well as areas involved in vigilance, cardiovascular regulation, and the mediation of motor activity.

Direct input to the LC, once thought to be extensive, has more recently been shown to be limited (see Aston Jones et al., Chapter 2, this volume, for review). The LC appears to receive direct input mainly from the nucleus paragigantocellularis (PGi) and the nucleus prepositus hypoglossi (Aston-Jones et al. 1986; Pieribone et al. 1987, 1988). These nuclei in turn receive sensory and autonomic input from a number of sources and may serve as relays to the LC (Andrezik et al. 1981; Van Bockstaele et al. 1988). In addition, there is evidence for parallel activation of the LC and the SNS by the PGi (Svensson 1988), suggesting that the LC and the SNS may serve, respectively, as the central and peripheral limbs of a catecholaminergic stress effector system (see Aston-Jones et al., Chapter 2, this volume, for review).

The other CNS noradrenergic system is the lateral tegmental system (LTS), consisting of two major groups of noradrenergic neurons, one medullary and one pontine (Moore and Bloom 1979). These areas innervate the basal forebrain, septal areas, the central amygdaloid nucleus (Fallon et al. 1978; Moore and Bloom 1979), and the paraventricular nucleus of the thalamus (Lindvall and Bjorklund 1974). These areas also receive input from the LC (Moore and Bloom 1979). The LTS provides noradrenergic input to the hypothalamus, and also innervates brain-stem areas other than associational and primary sensory nuclei (Moore and Bloom 1979), as well as sympathetic and somatic motor areas of the spinal cord (Westlund and Coulter 1980). The LTS appears to play a role in sympathoregulation (Granata et al. 1986), but its physiology is not completely understood.

Epinephrine

Adrenergic cells in the CNS are found in three brain-stem groups, designated C_1, C_2, and C_3 (Hokfelt et al. 1984). From these two nuclei, which are intermingled with noradrenergic cells, adrenergic neurons send projections to the hypothalamus, the nuclei of visceral efferent and afferent systems, the intermediolateral columns of the spinal cord, the periventricular re-

gion, and the LC (Cooper et al. 1986). These cell groups are thought to participate in autonomic and neuroendocrine regulation (Cooper et al. 1991).

Dopamine

The long-length dopaminergic systems include the mesocortical and mesolimbic projections, and the nigrostriatal pathway. The mesocortical system arises in the ventral tegmentum and substantia nigra, and projects to the prefrontal (including the supplementary motor area), cingulate, and entorhinal cortices. The mesolimbic system sends projections from these same origins to the septum, olfactory tubercle, nucleus accumbens, amygdala, and piriform cortex. The nigrostriatal pathway, which arises in these same areas and terminates in the caudate and putamen (see Cooper et al. 1986 for review), is involved in sensorimotor integration and control of motor output. Although their functions are not as well understood as those of the nigrostriatal dopaminergic projections, the mesolimbic and mesocortical dopaminergic systems also appear to be involved in sensorimotor integration. In these latter systems the information being integrated involves higher-order sensory representations and motivational or emotional states rather than information about muscle tone, limb position, and target location (Goldman-Rakic and Selemon 1990).

The intermediate-length systems include the tuberohypophyseal system, which originates in the arcuate and periventricular nuclei and projects to the intermediate pituitary lobe and to the tuberoinfundibular vascular system, which supplies the anterior pituitary lobe. These systems are involved in pituitary regulation. The incertohypothalamic system and the medullary periventricular group (including dopaminergic cells in the dorsal motor nucleus of the vagus, the nucleus tractus solitarius, and the tegmental radiation of the periaqueductal gray) are intermediate-length systems (Cooper et al. 1986) involved in neuroendocrine and possibly autonomic functions. Ultrashort dopaminergic systems in the brain include the periglomerular cells of the olfactory bulb and the interplexiform amicrine-like neurons that connect the inner and outer plexiform layers of the retina (Cooper et al. 1986) and are involved in primary sensory processing.

Table 1–1. DSM-III-R diagnostic criteria for posttraumatic stress disorder

A. The person has experienced an event that is outside the range of usual human experience and that would be markedly distressing to almost anyone, e.g., serious threat to one's life or physical integrity; serious threat or harm to one's children, spouse, or other close relatives and friends; sudden destruction of one's home or community; or seeing another person who Has recently been, or is being, seriously injured or killed as the result of an accident or physical violence.

B. The traumatic event is persistently reexperienced in at least one of the following ways:
   1. Recurrent and intrusive distressing recollections of the event (in young children, repetitive play in which themes or aspects of the trauma are expressed)
   2. Recurrent distressing dreams of the event
   3. Sudden acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative [flashback] episodes, even those that occur upon awakening or when intoxicated)
   4. Intense psychological distress at exposure to events that symbolize or resemble an aspect of the traumatic event, including anniversaries of the trauma

C. Persistent avoidance of stimuli associated with the trauma or numbing of general responsiveness (not present before the trauma), as indicated by at least three of the following:
   1. Efforts to avoid thoughts or feelings associated with the trauma
   2. Efforts to avoid activities or situations that arouse recollections of the trauma
   3. Inability to recall an important aspect of the trauma (psychogenic amnesia)
   4. Markedly diminished interest in significant activities (in young children, loss of recently acquired developmental skills such as toilet training or language skills)
   5. Feelings of detachment or estrangement from others
   6. Restricted range of affect, e.g., unable to have loving feelings
   7. Sense of a foreshortened future, e.g., does not expect to have a career, marriage, or children, or a long life

D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by at least two of the following:

(continued)

Table 1–1. DSM-III-R diagnostic criteria for posttraumatic stress disorder *(continued)*

1. Difficulty falling or staying asleep
2. Irritability or outbursts of anger
3. Difficulty concentrating
4. Hypervigilance
5. Exaggerated startle response
6. Physiologic reactivity upon exposure to events that symbolize or resemble an aspect of the traumatic event (e.g., a woman who was raped in an elevator breaks out in a sweat when entering any elevator)

E. Duration of the disturbance (symptoms in B, C, and D) of at least 1 month.

Specify delayed onset if the onset of symptoms was at least 6 months after the trauma.

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EFFECTS OF STRESS ON CATECHOLAMINERGIC SYSTEMS

Stressors of various types cause changes in central and peripheral catecholaminergic systems. The effects of stress exposure can vary depending on the brain area studied, the nature and chronicity of the stressor, and the species and strain of animal utilized. In many animal studies, acute stressors, particularly those that are uncontrollable, cause an increase in CNS norepinephrine and epinephrine release, with a consequent transient decrease in norepinephrine and epinephrine content in a number of brain areas (see Murburg et al. 1990 for review). With chronic stress, in most cases, compensatory increases in synthesis occur, so this decrease in content is not seen. Similarly, the number of CNS ß-adrenergic receptors decreases and the number of α_2-adrenergic receptors increases in a number of brain areas following chronic stress, probably in response to increased catecholamine levels (see Murburg et al. 1990 for review).

Stress effects on central dopaminergic systems are more com-

plex and less uniform, as described in detail by Dr. Zacharko in Chapter 5 of this volume. The nigrostriatal, mesolimbic, and mesoprefrontal systems—but not the mesopiriform, tuberoinfundibular, or tuberohypophyseal systems—manifest an increase in dopamine synthesis and catabolism in response to mild acute stress (Cooper et al. 1986). With chronic stress, the increase in dopamine turnover seen with acute stress is attenuated (see Chapter 5). Thus, in general, the transient depletion in catecholamine stores seen with acute stress exposure is not seen with chronic stress exposure because of compensatory mechanisms such as increased catecholamine synthesis and/or decreased catecholamine turnover that occur under conditions of chronic stress.

CATECHOLAMINES AND PTSD

The findings mentioned above indicating prominent changes in central catecholaminergic systems under conditions of acute and chronic stress in animals have suggested to many investigators that similar alterations may occur in patients with PTSD. This hypothesis is buttressed by recent clarifications in the anatomy and physiology of specific behaviors that are related to PTSD symptoms and are mediated in part by catecholamines. Examples of such symptoms are exaggerated startle response (see Rausch et al., Chapter 14, this volume); physiological reactivity—including increased activity of the SNS—to stimuli that resemble the etiological trauma (see McFall and Murburg, Chapter 7, and Murburg et al., Chapters 8 and 9); diminished interest in significant activities (see Zacharko, Chapter 5); difficulty with sleep and concentration, and hypervigilance (see Aston-Jones et al., Chapter 2); and possibly even flashbacks (see Charney et al., Chapter 6). This book constitutes a current compendium of much of the currently available data regarding involvement of catecholamine function in the pathophysiology of PTSD.

DIAGNOSTIC CRITERIA FOR PTSD

For those unfamiliar with the diagnostic criteria, or the cardinal symptoms, currently used in making the diagnosis of PTSD,

these criteria (American Psychiatric Association 1987) are detailed in Table 1–1. These symptoms may occur immediately or long after the precipitating event, and may persist for decades. Although we are far from being able to provide definitive treatment for PTSD, a number of approaches have been utilized with varying degrees of success. Both psychotherapeutic and biological interventions are humane and reasonable, although there is a great need for well-controlled studies of short- and long-term outcome, and both types of interventions may impact dually upon the psychology and biology of the disorder.

REFERENCES

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised. Washington, DC, American Psychiatric Association, 1987

Andrezik JA, Chan-Palay V, Palay SL: The nucleus paragigantocellularis lateralis in the rat: demonstration of afferents by the retrograde transport of horseradish peroxidase. Anat Embryol (Berl) 161:373–390, 1981

Aston-Jones G, Ennis M, Pieribone VA, et al: The brain nucleus locus coeruleus: restricted afferent control of a broad afferent network. Science 234:734–737, 1986

Axelrod J: The fate of noradrenaline in the sympathetic neurone. Harvey Lect 67:175, 1973

Berridge MJ: Cellular control through interactions between cyclic nucleotides and calcium. Advances in Cyclic Nucleotide Protein Phosphorylation Research 17:329–335, 1984a

Berridge MJ: Inositol triphosphate and diacylglycerol as second messengers. Biochem J 220:345–60, 1984b

Carlsson A: Monoamines of the central nervous system: a historical perspective, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven, 1987, pp 39–48

Cooper JR, Bloom FE, Roth RE: The Biochemical Basis of Neuropharmacology, 5th Edition. New York, Oxford University Press, 1986

Cooper JR, Bloom FE, Roth RE: The Biochemical Basis of Neuropharmacology, 6th Edition. New York, Oxford University Press, 1991

Fallon JH, Koziell DA, Moore RY: Catecholamine innervation of the basal forebrain, II: amygdala, suprarhinal cortex and enterorhinal cortex. J Comp Neurol 180:508–532, 1978

Goldman-Rakic PS, Selemon LD: New frontiers in basal ganglia research. Trends Neurosci 13:241–244, 1990

Granata AR, Numao Y, Kumada M, et al: A1 noradrenergic neurons tonically inhibit sympathoexcitatory neurons of the C1 area in rat brainstem. Brain Res 377:127–146, 1986

Harrison JK, Pearson WR, Lynch KR: Molecular characterization of alpha-1 and alpha-2 adrenoceptors. Trends Pharmacol Sci 12:62–67, 1991

Hillarp NA, Lagerstedt S, Nilson B: Isolation of granular fraction from suprarenal medulla, containing sympathomimetic catecholamines. Acta Physiol Scand 29:251–263, 1953

Hokfelt T, Johansson O, Goldstein M: Chemical anatomy of the brain. Science 225:1326–1334, 1984

Lindvall O, Bjorklund A: The organization of the ascending catecholamine neuron systems in the rat brain as revealed by the glyoxylic acid fluorescence method. J Comp Neurol 154:317–348, 1974

Milner JD, Wurtman RJ: Catecholamine synthesis: physiological coupling to precursor supply. Biochem Pharmacol 35:875–881, 1986

Moore RY, Bloom FE: Central catecholamine neural systems: anatomy and physiology of the norepinephrine and epinephrine systems. Annu Rev Neurosci 2:113–168, 1979

Murburg MM, McFall ME, Veith RC: Catecholamines, stress, and posttraumatic stress disorder, in Biological Assessment and Treatment of Posttraumatic Stress Disorder. Edited by Giller EL, Jr. Washington, DC, American Psychiatric Press, 1990, pp 29–64

Nagatsu T, Levitt M, Udenfriend S: Tyrosine hydroxylase: the initial step in norepinephrine biosynthesis. J Biol Chem 239:2910–2917, 1964

Nishizuka Y: Turnover of inositol phospholipids and signal transduction. Science 225:1365–1370, 1984

Pieribone VA, Aston-Jones G, Bohn MC, et al: Double labeling using fluorogold reveals neurotransmitter identity of afferents to locus coeruleus: a fluorescent double labeling study. Society for Neuroscience Abstracts 13:1458, 1987

Pieribone VA, Aston-Jones G, Bohn MC: Adrenergic and noradrenergic neurons in the C1 and C3 areas project to locus coeruleus: a fluorescent double labeling study. Neurosci Lett 85:297–303, 1988

Strange PG: Interesting times for dopamine receptors. TINS 14:43–45, 1991

Sunahara RK, Guan HC, O'Dowd BF, et al: Cloning of the gene for a human dopamine D_5 receptor with higher affinity for dopamine than D_1. Nature 350:614–619, 1991

Svensson TH: Peripheral regulation of locus coeruleus neurons: implications for drug effects. Paper presented at the 18th annual meeting of the Society for Neuroscience, Toronto, Ontario, November 1988

Van Bockstaele EJ, Pieribone VA, Aston-Jones G, et al: Anatomic evidence that autonomic and visceral areas converge on paragigantocellularis, a major afferent to locus coeruleus. Abstracts of the 18th annual meeting of the Society for Neuroscience, Toronto, Ontario, 1988, p 1318

Westlund KN, Coulter JD: Descending projections of the locus coeruleus and subcoeruleus/medial parabrachial nuclei in monkeys: axonal transport studies and dopamine-beta-hydroxylase immunocytochemistry. Brain Res Rev 2:235–264, 1980